

The University of Chicago

NEW SYNTHESSES OF DIETHYLSTILBESTROL AND HEXESTROL DIMETHYL ETHER

A PART OF A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

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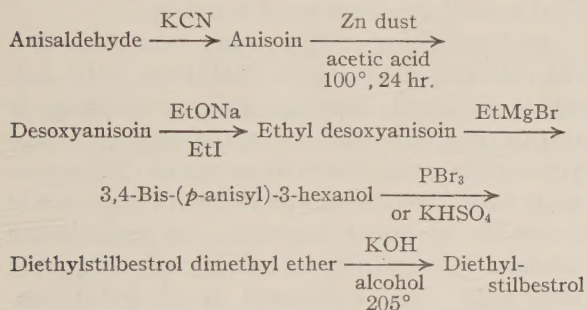
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Synthesis of Polyenes. III. A New Synthesis of Diethylstilbestrol

BY MORTON KLEIMAN¹

The *trans*-4,4'-dihydroxy- α,α' -diethylstilbene, now commonly referred to as diethylstilbestrol, was first synthesized in 1938 by Dodds and co-workers² by the following series of reactions

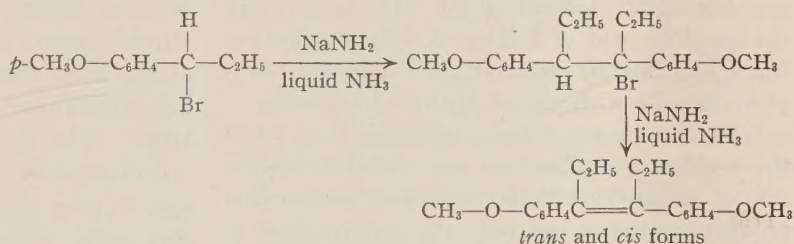


Numerous workers³ have since attempted to improve upon this method of preparation; however, all the other suggested syntheses are equally laborious and, in our estimation, inferior to Dodds' method from a practical standpoint (availability of raw materials, etc.).

In this Laboratory, the condensation of allyl

chloride and β -methylallyl chloride to hexatriene^{4a} and 2,5-dimethylhexatriene,^{4b} respectively, under the influence of sodamide in liquid ammonia has been studied exhaustively. The hypothesis evolved to account for these reactions suggested that a molecule such as anethole hydrobromide should react with sodamide or potassium amide to yield the products shown below.

Because of the possibility of side reactions, it was considered desirable to establish first the validity of the general method by the syntheses of the α,α' -dimethyl- and α,α' -diethylstilbenes from α -chloroethylbenzene and α -chloropropylbenzene, respectively.



α -Chloroethylbenzene, obtained by the addition of dry hydrogen chloride to styrene at low temperature, was treated with sodamide in liquid ammonia solution. When the sodamide was present in large excess, as was the case when the organic reactant was slowly added to the suspension of sodamide in liquid ammonia, a 40% yield of *cis*-dimethylstilbene was isolated. High boiling oils, the products of side reactions and poly-

(1) This paper is part of a dissertation submitted by Morton Kleiman to the Faculty of the Division of the Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy, March, 1942.

(2) Dodds, Goldberg, Lawson and Robinson, *Nature*, **141**, 247 (1938).

(3) (a) Kerschbaum, Kleedorfer, Prillinger, Wessely and Zajic, *Naturwiss.*, **27**, 131 (1939); (b) Wessely and Kleedorfer, *ibid.*, **27**, 567 (1939); (c) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940); (d) Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 93 (1940); (e) Kuwada, Sasagawa and Nisikawa, *ibid.*, **60**, 553 (1940); (f) Peteri, *J. Chem. Soc.*, 833 (1940).

(4) (a) Kharasch and Sternfeld, *J. Am. Chem. Soc.*, **61**, 2318 (1939); (b) Kharasch, Nudenberg and Sternfeld, *ibid.*, **62**, 2034 (1940).

TABLE I

The conclusions of the petrographer⁸ are that substances I and II are distinct from one another and from substances III and III'. Substances III and III' are probably identical.

Sub- stance	Crystallographic data	Optical data				Remarks
		Optical character	2V	N _p	N _g	
I	Orthorhombic	Biaxial	Near 70° (+)	>1.54, near 1.59	>1.73	Perfectly centered acute bisectrix figures, Z = b
II	Monoclinic	Biaxial	Small, near 15° (+)	...	...	
III	Monoclinic, twinning com- mon, crystals acicular	Biaxial	Very large, near 80-90°	<1.54, >1.52	>1.69	
III'	Monoclinic, twinning com- mon, crystals tabular	Biaxial	Very large, near 80-90°	<1.54	Near >1.65	

merization, were also obtained. No *trans*-dimethylstilbene was found among the products. When the order of addition was reversed, *i. e.*, when the sodamide was added to a solution of the organic reactant in liquid ammonia, 2-chloro-2,3-diphenylbutane was found in the reaction product, indicating the removal of only one molecule of hydrogen chloride. This substance, upon repeated distillation, lost a molecule of hydrogen chloride and was partially converted to *trans*- α, α' -dimethylstilbene. Analysis for halogen and conversion of the substance into 2,3-diphenylbutane by reduction with sodium in liquid ammonia established the identity of the intermediate chloro compound.

The synthesis of α, α' -diethylstilbene was attempted by the same method, namely, by treating α -chloropropylbenzene with sodamide in liquid ammonia. The addition of sodamide to a liquid ammonia solution of α -chloropropylbenzene yielded only a small amount of the intermediate 3-chloro-3,4-diphenylhexane and a large quantity of an unidentified oil. The presence of the small amount of 3-chloro-3,4-diphenylhexane was established by reducing the compound to diphenylhexane with sodium in liquid ammonia.

With the reverse order of addition, *i. e.*, when the α -chloropropylbenzene was added to an excess of sodamide in liquid ammonia, the reaction product contained not only the intermediate 3-chloro-3,4-diphenylhexane, but also an unsaturated oil at first believed to be diethylstilbene.

These observations indicated that, by reaction of α -chloropropylbenzene with sodamide in liquid ammonia, a condensation similar to that which occurs with α -chloroethylbenzene had taken place. The exact structure of the unsaturated oil formed was not ascertained,^{4a} however, because the sub-

stance could not readily be separated from the 3-chloro-3,4-diphenylhexane also formed in the reaction. Moreover, there is no agreement in the literature as to the physical constants of diethylstilbene,^{5,6,7} nor have its *cis* and *trans* forms been differentiated and characterized. Hence, it was also impossible to know whether the dibromo derivative obtained was the racemic or *meso* compound. Subsequent detailed study of the unsaturated reaction product obtained by similar condensation of anethole hydrobromide shed more light upon these questions of structure.

Anethole hydrobromide rather than the hydrochloride was used for condensations with sodamide in liquid ammonia because anethole is readily polymerized when treated with dry hydrogen chloride, even at low temperatures. When anethole hydrobromide was treated with an excess of sodamide in liquid ammonia, an unsaturated product (I) containing no halogen was isolated in 40% yield. This compound, after careful purification, melted at 120.5°. The *cis* form of diethylstilbestrol dimethyl ether is an oil. Addition of the *trans* form (II) (m. p. 124°) to (I) caused a significant lowering of the melting point of the latter. The non-identity of the two substances is confirmed by the comparison of their absorption spectra (Fig. 1) and their crystal forms (Table I). But when compound (I) was hydrogenated, the calculated amount of hydrogen was consumed, and a practically quantitative yield of dihydrodiethylstilbestrol dimethyl ether (III) (m. p. 142°) was obtained. This substance did not lower the

(5) Rising and Zee, *J. Am. Chem. Soc.*, **50**, 1706 (1928), described diethylstilbene as a solid, m. p. 89-90°, and its dibromide as a solid, m. p. 122-123°. The dibromo derivative obtained in this study melted at 166.5°.

(6) Ramart-Lucas and Anagnostopoulos, *Bull. soc. chim.*, [4] **43**, 1356 (1928), report that diethylstilbene is an oil, b. p. 168° (14 mm.).

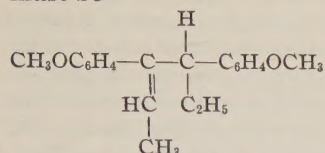
(7) Carlisle and Crawford, *J. Chem. Soc.*, 6 (1941), give the melting point of diethylstilbene as 70-71°.

(8) Dr. F. J. Pettijohn (Department of Geology, University of Chicago) to whom sincere thanks are here expressed.

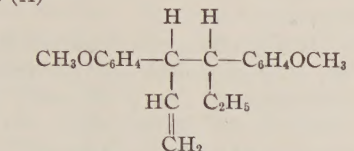
(4a) The possibility discussed in connection with formula (C) for compound (I), of a cyclic rather than an olefinic structure, may well be considered. The same applies to some of the supposed diethylstilbenes reported in references 5, 6 and 7. This problem is being further investigated.

melting point of a known sample (III') of dihydrodiethylstilbestrol dimethyl ether.

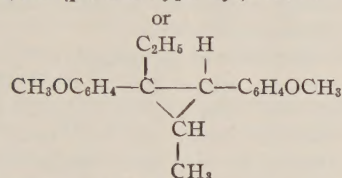
Since substance (I) is not diethylstilbestrol dimethyl ether, but gives dihydrodiethylstilbestrol dimethyl ether when hydrogenated, its formula must be



Two racemic pairs
cis and *trans* (A)



Two racemic pairs (B)
3,4-di-(*p*-methoxyphenyl)-hexene-1



(C) 1-methyl-2,3-di-(*p*-methoxyphenyl)-3-ethylcyclopropane

Both the *cis* and *trans* racemic forms of (A) have been described:^{3b} one is an oil; the other, a solid

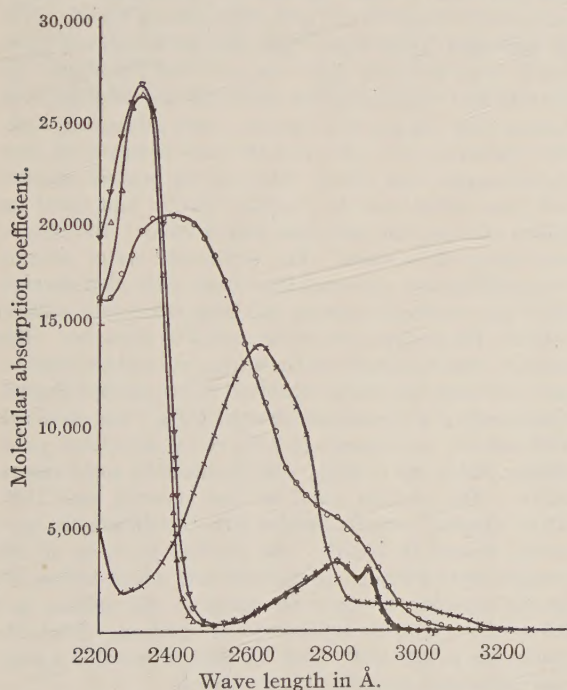


Fig. 1.—Absorption spectra: Δ , dihydrostilbestrol dimethyl ether; ∇ , (Compound I); $\circ$, diethylstilbestrol dimethyl ether; $\times$, anethole.

melting at 50°. Formula (B) or (C) is therefore assigned to (I). A compound of either formula should have an absorption spectrum very much like that of dihydrodiethylstilbestrol dimethyl ether. Figure 1 shows this to be the fact.

Two hydrogenation products of (C) are geometrically possible, but energetic effects of substituents would probably favor one over the other.

Demethylation of (I) by potassium hydroxide in glycol at 225° gave two products, a solid and an oil. The solid was identified as the 4,4'-dihydroxy- α,α' -diethylstilbene (diethylstilbestrol). When it was mixed with an authentic sample of this substance, its melting point was not depressed, nor was there any depression in the melting points of mixtures of the diacetate and the dibenzoate of this substance with authentic samples of diethylstilbestrol diacetate and dibenzoate, respectively. As a further confirmation, the absorption spectrum of the diethylstilbestrol derived from (I) was found to be identical with that of an authentic sample of diethylstilbestrol (Fig. 2).

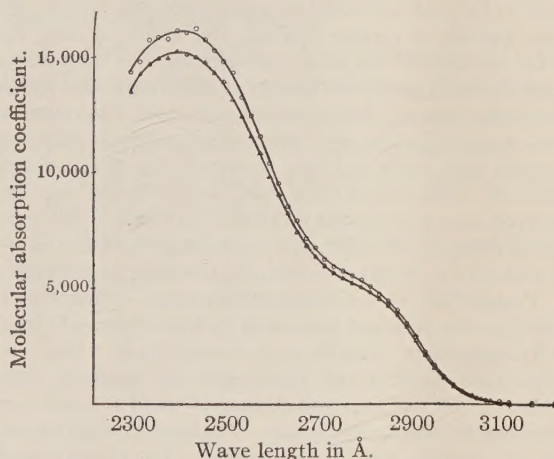


Fig. 2.—Absorption spectra: $\circ$, highly purified sample of diethylstilbestrol; Δ , sample of diethylstilbestrol obtained from demethylation of compound (I).

These results suggest that in the conversion of (II) to diethylstilbestrol, rearrangement of the double bond or cleavage of the cyclopropane ring and demethylation occurred simultaneously.

When two moles of anethole hydrobromide in liquid ammonia was treated with one mole of sodamide, followed by one mole of sodium, an 80% yield of the corresponding amine (1-amino-1-[*p*-methoxyphenyl]-propane) was obtained.

Experimental

Preparation of α -Chloroethylbenzene.—Fifty grams of redistilled styrene (b. p. 40° (12–13 mm.)) was cooled to

—80° and dry hydrogen chloride was passed in until the gain in weight was 28 g. The reaction mixture was warmed slowly to room temperature and was then distilled at 11 mm. pressure (b. p. 73°). The yield of α -chloroethylbenzene was 48.5 g. (68%).

Preparation of 2-Chloro-2,3-diphenylbutane.—Ten grams of α -chloroethylbenzene (0.07 mole) was dissolved in liquid ammonia, and 4 g. of sodamide⁹ (0.1 mole) added in portions. The reaction mixture was vigorously agitated. At the end of one and one-half hours, the ammonia was removed; the residue was taken up in water and extracted several times with ether. The combined ether extracts were dried over calcium chloride and, after removal of the ether, distilled at low pressure. After several distillations, a fraction boiling at 147–148° (11 mm.) was obtained. This oil was shown to contain 2-chloro-2,3-diphenylbutane by analysis for halogen and by the fact that when treated with sodium in liquid ammonia, it gave 2,3-diphenylbutane (m. p. 124°).

A portion of the above oil lost hydrogen chloride after repeated distillation *in vacuo*, and upon standing, deposited crystals of *trans*-dimethylstilbene. The latter, after crystallization from methyl alcohol, melted at 105°.

Preparation of *cis*-Dimethylstilbene.—Twenty grams of α -chloroethylbenzene, diluted with an equal volume of toluene, was added slowly to a vigorously agitated suspension of 24 g. of sodamide⁹ in liquid ammonia. When the first portion of organic reactant was added, a deep red color developed; this color was discharged by each subsequent portion, and each time gradually reappeared in the reaction mixture. At the end of two hours, the ammonia was removed; the residual reaction mixture was first treated with water and then extracted several times with toluene. The extract was dried over calcium chloride, filtered, and fractionated at 10 mm. pressure. The fraction boiling at 135–156° was crystallized from methanol; it yielded 6 g. (40%) of *cis*-dimethylstilbene, m. p. 66–67°.

Preparation of α -Chloropropylbenzene.—Phenylethylcarbinol was prepared (according to Meisenheimer¹⁰) from ethylmagnesium bromide and benzaldehyde. The carbinol thus obtained was treated with dry hydrogen chloride at 0° for one hour and allowed to stand at room temperature for twenty-four hours. The layer of water formed in the reaction was then separated. The oil was dried over calcium chloride and twice distilled, b. p. 85–87° (15 mm.). The yield of the chloropropylbenzene (based upon the amount of carbinol used) was 55%.

Reaction of α -Chloropropylbenzene with Sodamide in Liquid Ammonia.—To a vigorously stirred suspension of 0.3 mole of sodamide in liquid ammonia was added drop by drop 15 g. (0.1 mole) of α -chloropropylbenzene diluted with an equal volume of toluene. During the addition, there was developed a light purple color which gradually became darker, finally changing to a deep orange-red. The stirring was continued for one-half hour after the addition of the organic reactant had been completed; then the ammonia was removed by evaporation. The reaction mixture was treated with small portions of water, chilled in an ice-salt bath, and acidified. The toluene layer, was

next separated. Several extractions with toluene were made, and the combined toluene extracts were dried over calcium chloride. The toluene was removed at reduced pressure, and the residue distilled at 12 mm. Small amounts at the beginning and at the end of the distillation were discarded. Most of the material distilled at 162–164°. Eleven grams of product was obtained.

When a portion of this material was dissolved in carbon tetrachloride and treated with a solution of bromine in the same solvent, the bromine was rapidly decolorized. Evaporation of the solvent left a solid residue which was crystallized several times from high-boiling ligroin. The compound thus obtained melted at 166.5°.

Anal. Calcd. for $C_{13}H_{20}Br_2$: Br, 40.36. Found: Br, 40.66.

Hydrogenation of a second portion of the reaction product in ethyl alcohol over platinum black yielded a 3,4-diphenylhexane, m. p. 88.5–89°. Treatment of a third portion of the reaction product with sodium in liquid ammonia also yielded 3,4-diphenylhexane. The reaction product was thus shown to contain an unsaturated compound, supposedly diethylstilbene, and the intermediate diphenylchlorohexane.

Synthesis of Compound (I).—Fifty grams of redistilled anethole, diluted with an equal volume of toluene and kept at –80°, was allowed to absorb 27.5 g. of dry hydrogen bromide (one to one mole ratio). Some of the anethole crystallized, but soon redissolved. To remove any excess hydrogen bromide, the reaction vessel was first evacuated by a water pump, then a stream of dry carbon dioxide was passed through the mixture maintained at –80°. The toluene solution of anethole hydrobromide was then added in small portions to a suspension of 40 g. of sodamide in about 700 cc. of liquid ammonia (contained in an unsilvered Dewar flask). The mixture was stirred vigorously. The following color changes were observed: the mixture was yellowish-green after the first addition, but became deep red in a few minutes; each subsequent addition discharged the color, and the same sequence of color changes again took place. After all the organic reactant had been added and the reaction mixture had stood for fifteen minutes, the ammonia was removed; the residue was taken up in water. The well-cooled water solution was acidified and extracted four times with ethyl acetate. After the combined extracts had been dried over calcium chloride, the drying agent was removed by filtration. The solvents were distilled from the filtrate at reduced pressure, and the remaining oil was dissolved in hot methyl alcohol. Upon cooling, a crystalline material (17 g.) was obtained. This amount corresponds to 34% of the calculated yield. Higher yields, up to 40%, were obtained in some experiments. The melting point of the material was 118°. After repeated recrystallization from methanol, the substance melted at 120.5°. The residual products of this reaction were polymerized anethole and a high-boiling oil. In one experiment, ether was added to this residue, and 3.3 g. of a crystalline substance was obtained. This substance (m. p. 209–210°; mol. wt. 870) is probably a polymer containing six molecules of anethole.

Hydrogenation of Compound (I).—One-half gram of compound (I) dissolved in methyl alcohol was hydrogenated with the aid of platinum black catalyst. The

(9) Vaughn, Vogt and Nieuwland, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

(10) Meisenheimer, *Ann.*, **446**, 80 (1926).

calculated amount of hydrogen was absorbed, and recovery of the hydrogenated product was practically quantitative. After crystallization from methanol, 0.45 g. of material was obtained, m. p. 142°.

Demethylation of Compound (I): Preparation of Diethylstilbestrol.—Two grams of compound (I), 5 g. of potassium hydroxide, and 30 cc. of ethylene glycol were sealed in a heavy Pyrex bomb tube at 10^{-5} mm. pressure, and heated at 224° for eighteen hours. After cooling and opening the bomb tube, the reaction mixture was diluted with water, filtered to remove silica, acidified with dilute hydrochloric acid, digested for a short time on the steam-bath, and finally cooled to 0°. The solid which separated was collected on a filter. This crude product was crystallized several times from benzene. By these operations it was separated into a solid and an oil. The solid melted at 165–166°. Its identity with diethylstilbestrol was established by the following criteria: (1) the preparation of the diacetate; (2) the preparation of the dibenzoate; (3) the fact that no depression in melting point was observed when the solid was added to an authentic sample of diethylstilbestrol. The diacetate of this material (crystallized from high-boiling ligroin) melted at 120°. The dibenzoate (crystallized from a mixture of high-boiling ligroin and benzene) melted at 209–211°.

When the residual oil (from the bomb tube reaction) was treated in a sealed tube at 224° with 1.5 g. of potassium hydroxide in 8 cc. of ethylene glycol (as in the first operation), it gave an additional amount of diethylstilbestrol. The total yield of the latter was 1.1 g., or 55.5% of the amount calculated from the weight of compound (I) used.

Preparation of 1-Amino-1-(*p*-methoxyphenyl)-propane.—Anethole hydrobromide (prepared from 20 g. of redistilled anethole according to the directions already described) was poured into liquid ammonia contained in an unsilvered Dewar flask; 2.7 g. of sodamide was then added. After stirring for two hours, a slight excess of sodium was

added in small portions. When the excess sodium had reacted with the liquid ammonia (as evidenced by the disappearance of the characteristic blue color), the ammonia was removed by evaporation. The reaction mixture was taken up in water; the solution was made acid and extracted with toluene. Only a minute amount of brown oil was obtained by evaporation of the toluene; this was discarded. The acid aqueous solution was made alkaline with sodium hydroxide and extracted several times with toluene. The combined toluene extracts were dried with a small amount of "Drierite." After the drying agent had been removed by filtration, dry hydrogen chloride was passed into the filtrate. The solid which separated was collected on a filter and purified by solution in absolute alcohol, addition of absolute ether to the solution, and cooling. A snow-white, crystalline material melting at 215° (with decomposition) was thus obtained. The benzoyl derivative of this substance was prepared by the Schotten-Baumann method. When crystallized from aqueous alcohol, it melted at 120°. The total yield of amine hydrochloride was 21 g., or 80% of the amount calculated.

Summary

1. The reactions of α -chloroethylbenzene and α -chloropropylbenzene with sodamide in liquid ammonia have been studied.
2. The preparation of a compound (I) believed to be either 3,4-di-(*p*-methoxyphenyl)-hexene-1 or 1-methyl-2,3-di-(*p*-methoxyphenyl)-3-ethylcyclopropane in 40% yield is described.
3. The preparation of diethyl stilbestrol from (I) has been accomplished.
4. The preparation of 1-amino-1-(*p*-methoxyphenyl)-propane is given.

Factors Determining the Course and Mechanism of Grignard Reactions. VI. A New Synthesis of Hexestrol Dimethyl Ether (3,4-Dianisylhexane)

BY MORTON KLEIMAN¹

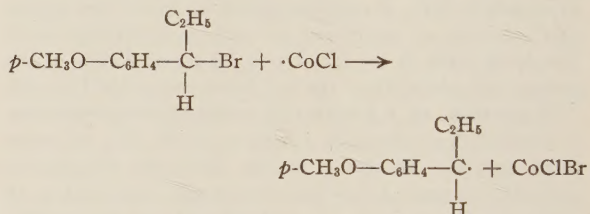
Introduction

Hexestrol was first isolated from the demethylation products of anethole. Bioassays of the principal product, anol, indicated that the material contained a powerful estrogenic impurity [3,4-bis-(*p*-hydroxyphenyl)-hexane]. The name hexestrol, proposed for this compound, is now commonly used.

The earlier methods for the synthesis of hexestrol involve the use of intermediates which are difficult to prepare; the yields, moreover, are poor.² Better results (7 to 20% over-all yields) are claimed for the coupling action of metals on anethole hydrobromide.^{2,3}

Reaction of Anethole Hydrobromide with Grignard Reagents in the Presence of Cobaltous Chloride.—Previous work in this Laboratory⁴ has indicated that cobaltous chloride reacts with Grignard reagents to yield a cobalt subhalide (CoCl) which reduces many organic halides to organic free radicals. Hence, it was assumed that a chain reaction might take place when anethole hydrobromide is treated with a Grignard reagent, (*e. g.*, phenyl- or methyl-

magnesium bromide) in the presence of cobaltous chloride. One step in this chain is the reaction



The dimerization of these free radicals was anticipated because it has already been demonstrated⁵ that weakly electronegative radicals have a strong tendency to dimerize.

When a well-cooled ether-toluene solution of anethole hydrobromide was added slowly to a cooled solution of phenylmagnesium bromide in ether containing cobaltous chloride (5 mole per cent.), a vigorous reaction took place. The reaction mixture yielded 42% of hexestrol dimethyl ether (m. p. 142°). The yield was somewhat lower when methylmagnesium bromide was used. Ferrous chloride and nickelous chloride are also catalysts for the desired reaction, but are not as effective as cobaltous chloride. Chromic, manganous, cupric and cuprous chlorides are totally ineffective.

Experimental

The methylmagnesium bromide was prepared as follows. Seventy-five grams of pure magnesium was covered

(1) The author wishes to express his appreciation to E. I. du Pont de Nemours & Company, Wilmington, Delaware, for support which made this work possible.

(2) For a literature review dealing with this subject, see Docken and Spielman, *J. Am. Chem. Soc.*, **62**, 2163 (1940).

(3) Short, British Patent 523,320; *Chem. and Ind.*, **59**, 703 (1940); Bernstein and Wallis, *J. Am. Chem. Soc.*, **62**, 2871 (1940); Girard and Sandulesco, French Patent 855,879 (May 22, 1940).

(4) For earlier references, see Kharasch and Fields, *J. Am. Chem. Soc.*, **63**, 2316 (1941).

(5) Kharasch and Sayles, unpublished work.

with one liter of pure, dry ether and methyl bromide gas was passed into the mixture. Reaction set in after a short time. The methyl bromide was introduced at a rate sufficient to keep the ether gently refluxing, and, at the end of two hours, more ether was added to replace that lost by evaporation. When the magnesium was all dissolved, stirring and refluxing were continued for ten minutes; then the mixture was allowed to stand for twenty-four hours. The solution of the Grignard reagent was next filtered through a plug of glass wool into a dark bottle fitted with a siphon and a calcium chloride tube. Samples of 4 to 5 ml. of the Grignard reagent were used for analysis by titration. The proper aliquots were withdrawn for each reaction.

The phenylmagnesium bromide was similarly prepared from 48 g. of pure magnesium, one liter of dry ether, and 300 g. of phenyl bromide.

Preparation of Anethole Hydrobromide.—Fourteen and eight-tenths grams of anethole (0.1 mole) was diluted with two and one-half times its volume of dry toluene and cooled to -80° while dry hydrogen bromide (8.1 g., 0.1 mole) was passed into the solution. This solution was next allowed to warm up to 0° while a stream of dry carbon dioxide was bubbled through it to displace unreacted hydrogen bromide. Finally, the solution was degassed at 0° by evacuation of the reaction vessel. The solution of anethole hydrobromide thus obtained was diluted with an equal volume of absolute ether, immediately cooled again to -80° , and kept at that temperature. For the subsequent reactions, it was siphoned directly into the Grignard reagent mixture.⁶

Apparatus for the Grignard Reactions.—The apparatus consisted of a 500-cc. four-necked, round-bottom flask equipped with a mercury-sealed stirrer, a reflux condenser fitted with a calcium chloride tube, an adapter for addition of the catalyst, and a siphon tube through which the anethole hydrobromide was added.

Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride (5 mole per cent.).—To 65 cc. of 2.3 *M* ethereal phenylmagnesium bromide solution (0.15 mole) cooled in a bath at -20 to -10° and vigorously stirred, was added 1.0 g. of anhydrous cobaltous chloride (5 mole per cent.). The mixture became brownish-black. Anethole hydrobromide solution (0.1 mole) was next added in small portions over a period of one-half hour. During this time the reaction mixture was maintained at -20 to -10° . It was then allowed to warm to room temperature, and stirring was continued for a few hours.

At the end of this time, the reaction mixture was poured onto a mixture of 300 g. of ice and 10 cc. of concentrated hydrochloric acid. After separation of the organic layer, the aqueous solution was extracted twice with benzene. The organic extracts were combined and dried with calcium chloride. The solvents were removed by distillation, and the residue (a greenish-black oil which solidified on cooling) was crystallized twice from methyl alcohol. The yield was 6.1 g. (41%) of hexestrol dimethyl ether which melted sharply at 142° . No depression in melting point was

observed when this compound was mixed with an authentic sample of hexestrol dimethyl ether.

The residue from the reaction mixture yielded 6.0 g. of biphenyl, m. p. $68-69^{\circ}$, and some high-boiling material. The amount of biphenyl obtained corresponds very nearly to a 40% conversion of the Grignard reagent to biphenyl.

Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride (15 mole per cent.).—The above reaction was repeated using 15 mole per cent. cobaltous chloride. One-third of this chloride was added at the beginning of the reaction; the remainder was added in small portions continuously during the addition of the anethole hydrobromide solution. The reaction mixture was worked up in the manner already described; the yield of hexestrol dimethyl ether was 4.0 g. (27%).

Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Nickelous Chloride (5 mole per cent.).—The procedure in carrying out this reaction was the same as that described above. One gram (5 mole per cent.) of anhydrous nickelous chloride used as a catalyst was added gradually during the course of the reaction. The yield of hexestrol dimethyl ether was 2.1 g. (14%).

Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Ferric Chloride (5 mole per cent.).—The procedure in this reaction was the same as that described above. The catalyst, 0.8 g. of anhydrous ferric chloride (5 mole per cent.), was all added at the beginning of the reaction because of the tendency of ferric chloride to become sticky in the presence of ether vapor. The yield of hexestrol dimethyl ether was 4.3 g. (29%).

Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of other Metal Halides.—Attempts were made to obtain hexestrol dimethyl ether by reaction of anethole hydrobromide with phenylmagnesium bromide in the manner described above; in each instance 5 mole per cent. of one of the following metal halides was used as a catalyst: chromic chloride, manganous chloride and cupric chloride. No hexestrol dimethyl ether was found among any of the reaction products.

Reaction of Anethole Hydrobromide with Methylmagnesium Bromide in the Presence of Cobaltous Chloride (15 mole per cent.).—The reaction was carried out in the usual manner. One-third of the catalyst was added at the beginning of the reaction, the remainder in small portions at intervals during the addition of the anethole hydrobromide solution. The yield of hexestrol dimethyl ether was 4.0 g. (27%).

Summary

1. Hexestrol dimethyl ether has been prepared from anethole hydrobromide and Grignard reagents in the presence of a halide of cobalt, nickel or iron.

2. A mechanism to account for the catalytic effect of these metallic halides on the reaction of anethole hydrobromide with Grignard reagents is suggested.

(6) It was found that the desired product is best obtained by adding the anethole hydrobromide solution to the Grignard reagent, rather than by the reverse order of addition.

3. The halides of chromium, manganese and copper were found to be ineffective as catalysts in the synthesis of hexestrol dimethyl ether from anethole hydrobromide and Grignard reagents.

